REMARKS

After entry of this amendment, claims 1, 3-5, 7-33, 35-36 and 38-45 are pending. Claims 1, 3, 33, and 35 are amended.

35 U.S.C. 102 Rejection Over Deegan et al.

Reconsideration is respectfully requested of the rejection of claims 1, 3-4, 8, 17-25, 30-33, and 35-36 as anticipated by Deegan et al., *Toxicology* **1994**, *89*, 1-14. The Office asserts that "if the prior art teaches the identical chemical structure, the properties Applicant discloses and/or claims are necessarily present."[1] While Applicant may agree with the Office's assertion with respect to composition claims, the claims at issue are directed to methods of treatment and not to compositions. Further, to the extent that the Office's assertion of anticipation by the Deegan et al. reference relies on inherency, this reliance is improper. As stated in MPEP §2131, a claim is anticipated under 35 U.S.C. §102 only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.

Claims 1 and 31

Claim 1 is directed to a method for preventing or reducing the incidence of ototoxicity in a patient selected from the group consisting of a human, a cat, and a dog undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound, the method comprising administering to said patient an effective amount of an otoprotective agent comprising methionine. Claim 31 also generally requires these elements.

Deegan et al. generally describe the nephrotoxicity, cytotoxicity, and renal handling of a cisplatin-methionine complex. The Deegan reference discloses that when the cisplatin-methionine complex is administered, cisplatin-induced nephrotoxicity is not exhibited in Wistar rats. Also, Deegan et al. found that cisplatin is a substrate for the organic base transport system (evidenced by net renal secretion) while a cisplatin-methionine complex is not such a substrate (evidenced by secretion by filtration only).

[1] See page 3 of the Office action dated January 19, 2007.

Deegan et al. also state that this function as a substrate for organic base transport system may be the determinant factor for nephrotoxicity.[2]

Deegan et al. do not disclose the element of "a patient selected from the group consisting of a human, a cat, and a dog" because they exclusively administer the cisplatin-methionine complex to Wistar rats. Accordingly, claims 1, 31, and the claims that depend therefrom are not anticipated by Deegan et al.

Claim 33

Claim 33 is directed to a method for preventing or reducing the incidence of ototoxicity in a patient undergoing treatment with an aminoglycoside antibiotic, the method comprising administering to said patient an effective amount of an otoprotective agent comprising methionine. As described above, a claim is anticipated under 35 U.S.C. §102 only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. For claim 33, the element of a "patient undergoing treatment with an aminoglycoside antibiotic" is not disclosed by Deegan et al. Deegan et al. solely report the nephrotoxic and antineoplastic effects of the cisplatin-methionine complex. Deegan et al. do not disclose treatment with an aminoglycoside antibiotic. Thus, claim 33 and the claims that depend therefrom are not anticipated by Deegan et al.

35 U.S.C. § 103 Rejection Over Kowbata et al. in view of Deegan et al. and Ormond et al.

Reconsideration is respectfully requested of the rejection of claims 1, 3-5, 7-33, 35-36, and 38-45 as unpatentable over Kowbata et al. (U.S. 5,466,678) in view of Deegan et al. and further in view of Ormond et al. under 35 U.S.C. § 103(a). The Office asserts that it

> would be inherent that S-adenosyl-L-methionine would prevent ototoxicity caused by a platinum complex compound, since a patient receiving a platinum complex compound is at risk for both nephrotoxicity and

[2] Deegan et al., *Toxicology* **1994**, *89*, at page 12.

> ototoxicity and using S-adenosyl-L-methionine to reduce nephrotoxicity would at the same time also prevent ototoxicity caused by the platinum complex compound.[3]

Claims 1 and 31

Claim 1 is described in more detail above and has been amended to require an otoprotective agent comprising methionine so claim 1 does not read on the administration of S-adenosyl-L-methionine. Thus, the issue now is whether it would have been obvious to treat cisplatin-induced ototoxicity by administration of methionine.

Inherency has no relevance to obviousness of a method claim that is directed to treatment of another condition unrecognized in the prior art. As the C.C.P.A has stated in reversing a rejection of a method of treatment claim for inherency in what was acknowledged to be an obvious combination of references:

> [Inherency] is quite immaterial if, as the record establishes here, one of ordinary skill in the art would not appreciate or recognize that inherent result, *in re Shetty*[4]

The method claims at issue in *Shetty* were directed to methods for appetite control and the cited prior art disclosed compounds and dosages useful for combating microbial infestation. The *Shetty* court stated that the Office had "failed to show a reasonable expectation, or some predictability" that the prior art compound disclosed in the first reference would be an effective appetite suppressant if administered in the dosage disclosed in the second reference and that the Office's hindsight assertion that the dosages would make the weight loss method obvious was insufficient.[5] Similar to *Shetty*, claims 1 and 31 recite a method for preventing or reducing the incidence of ototoxicity while the references cited against these claims disclose methods for reducing the incidence of nephrotoxicity. Thus, claims 1 and 31 are patentable over the cited references.

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[3] Pages 4-5 of the Office action dated January 19, 2007.
[4] 195 U.S.P.Q. 753.
[5] See id. at 756.

Further, the court in *Ex parte Zbornik* found a process for treating Air Sac Infection in fowl patentable over prior art disclosing substantially the same compound to treat ducks for malaria.[6] The *Zbornik* court found that the claims were patentable because the cited reference was not concerned with appellant's problem and it failed to suggest its solution. Similarly, the cited references are concerned with reducing nephrotoxicity, not ototoxicity, and they fail to suggest to a skilled person that methionine would provide otoprotection to a patient undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound.

Kowbata et al. merely disclose that administration of S-adenosyl-L-methionine (SAMe) with cisplatin reduces the nephrotoxicity known to arise from cisplatin administration. The reference does not disclose nor suggest that SAMe or any other composition would inevitably be effective to protect against ototoxicity. The text of Kowbata contains no mention of ototoxicity. To the extent it has any relevance at all, the reference would have led a person of ordinary skill to believe that SAMe was only effective as a nephroprotectant.[7]

Furthermore, if it would not have been obvious that SAMe was an effective otoprotectant, it certainly would not have been obvious from the Kowbata reference that methionine was an effective otoprotectant. There is much evidence that different otoprotective agents have different therapeutic mechanisms and as such may or may not be effective for a specific mechanism of ototoxicity. This knowledge of the differences in mechanisms for different causes and otoprotective agents would not have

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[6] *Ex parte Zbornik*, 109 U.S.P.Q. 508.

[7] For example, Kowbata et al. state

> ...SAMe, when administered intravenously, concentrates specifically at the renal tissue, where it is converted through the process of transmethylation to S-adenosylhomocysteine...which in turn is converted to such compounds as homocysteine, cysteine and glutathione. It was also noted that there was no increase in the blood level of these SH-compounds after the SAMe administration.

Also, the data in Table I of Example 4 shows a significant increase in SH compounds in the renal tissue, but not a significant increase in these compounds in the blood plasma. Generally, for a protectant compound to be effective against ototoxicity, it must reach the cochlea. Consequently, because the distribution studies showed SAMe did not significantly increase the blood plasma levels of SH compounds, it would not have been obvious to a person of ordinary skill upon a reading of the Kowbata reference that SAMe would be an effective protectant for ototoxicity caused by cisplatin exposure.

led one of ordinary skill from the use of S-adenosyl-L-methionine as a nephroprotectant for cisplatin administration to the use of methionine as an otoprotectant for cisplatin exposure.

Further, Deegan et al. and Ormond et al. do not remedy the deficiencies of Kowbata. The Deegan et al. reference is described in more detail above. Ormond et al. generally describe reduced nephrotoxicity of a cisplatin-methionine complex and makes the observations that the reduced nephrotoxicity of the cisplatin-methionine complex as compared to cisplatin alone may be because the cisplatin-methionine complex is not being transported by the renal proximal tubule. Thus, Deegan and Ormond both describe the nephroprotective mechanism of methionine as forming a complex with the cisplatin wherein this cisplatin-methionine complex is not handled by the kidneys in the same way as cisplatin alone.

Moreover, even with the benefit of hindsight, administration of an inherently ototoxic dosage of cisplatin cannot be demonstrated in any method suggested by the combination of cited references. Even in the context of novelty under §102, inherency may not be established if there is only a probability or possibility that a certain result may occur.[8] Certainly, no less a standard can apply with respect obviousness under §103 where the actual teachings of the references are relatively more remote than in the case of novelty. In the present case, administration of cisplatin in accordance with the combined disclosures would not have necessarily and inevitably resulted in the occurrence of ototoxicity in a subject. As explained above, Kowbata describes the effects of SAMe on nephrotoxicity and Deegan et al. and Ormond et al. merely describe the renal handling of the cisplatin-methionine complex. There is no disclosure that the doses of cisplatin administered would provide more than a mere possibility that some of those subjects might also suffer from ototoxicity. Also, in 1995, the human doses of cisplatin included 20 mg/m^2 I.V. daily for 5 days every three weeks and single does of 50-100 mg/m^2 every 4 weeks.[9] It was further reported that nephrotoxicity was the

[8] *In re Oelrich*, 666 F.2d 578.
[9] Platinol-AQ Data Sheet, January 1995.

"major dose-limiting toxicity of Platinol" (Platinol is an aqueous solution of cisplatin)[10] Additionally, it was reported that nephrotoxicity occurred in about 28-36% of patients given a single dose of 50 mg/m^2 cisplatin and ototoxicity occurred in up to about 31% of patients given the same 50 mg/m^2 cisplatin dose.[11] In other studies, fewer patients experienced ototoxicity (e.g., clinical hearing loss) than nephrotoxicity.[12] In these reports, the majority (69% in one report) did not experience ototoxicity. Thus, there is not more than a mere possibility that ototoxicity will occur for many therapeutic doses of cisplatin and ototoxicity certainly does not inevitably or necessarily result upon the administration of cisplatin in the range of doses disclosed in the cited references. Therefore, claims 1, 31, and the claims that depend therefrom satisfy the requirements of 35 U.S.C. § 103(a).

Claim 33

Claim 33 is described in more detail above. To establish a prima facie case of obviousness, the prior art reference (or references when combined) must teach all or suggest all the claim limitations.[13] For claim 33, the element of a "patient undergoing treatment with an aminoglycoside antibiotic" is not disclosed by Deegan et al. None of the cited references teach or suggest treatment with an aminoglycoside antibiotic. Accordingly, claim 33 and the claims that depend therefrom satisfy the requirements of 35 U.S.C. § 103(a).

35 U.S.C. § 112 Rejections

Further reconsideration is respectfully requested of the rejection of claims 3-5, 7-33, 35-36, and 38-45 under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement. The claims recite a method for "preventing or reducing the incidence of ototoxicity" in a patient undergoing treatment with either an anti-tumor platinum-coordination compound or an aminoglycoside antibiotic. While the Office

[10] See id.
[11] See id.
[12] Planting et al., Cancer Chemotherapy and Pharmacology 1997, 40(4), 347-352.
[13] See MPEP § 2143.

states that the "[i]t is not seen from the data in the specification that the compound of the claims can be used to treat ototoxicity,"[14] applicant respectfully submits that the present amendments overcome this rejection and the amended claims satisfy the 35 U.S.C. § 112.

Further, the Office asserts that "a preventative measure has not yet been established somewhat in light of the issues concerning delivery of active agents."[15] The Office describes the delivery methods of other protective agents as impractical. However, delivery of the claimed otoprotective agents is not impractical; particularly, D-methionine can be administered parenterally, orally, and to the round window membrane and is known to be safe for human administration over a wide range of dosages. Also, because a person of skill in the art would know how to use the invention as described in human patients and the instant application shows otoprotection in animals, the instant claims satisfy the enablement requirement of 35 U.S.C. § 112.

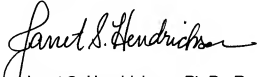
[14] Page 6 of the Office action dated January 19, 2007.
[15] Page 7 of the Office action dated January 19, 2007.

CONCLUSION

Applicant submits that the present application is now in a condition for allowance and requests early allowance of the pending claims.

The Commissioner is hereby authorized to charge any under payment or credit any over payment to Deposit Account No. 19-1345.

Respectfully submitted,



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